REVIEW ARTICLE

Electromagnetic navigation bronchoscopy: A descriptive analysis

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ABSTRACT Electromagnetic navigation bronchoscopy (ENB) is an exciting new bronchoscopic technique that promises accurate navigation to peripheral pulmonary target lesions, using technology similar to a car global positioning system (GPS) unit. Potential uses for ENB include biopsy of peripheral lung lesions, pleural dye marking of nodules for surgical wedge resection, placement of fiducial markers for stereotactic radiotherapy, and therapeutic insertion of brachytherapy catheters into malignant tissue. This article will describe the ENB procedure, review the published literature, compare ENB to existing biopsy techniques, and outline the challenges for widespread implementation of this new technology.

KEY WORDS Electromagnetic navigation bronchoscopy; global positioning system; surgical wedge resection; stereotactic radiotherapy; brachytherapy

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Introduction

Peripheral pulmonary lesions (PPLs) are common incidental findings (1). Their rising incidence has paralleled the increasing use of computed tomography (CT) as CT is approximately three times more sensitive than plain chest radiography (CXR) scans. Detection of PPLs will further increase should the community embrace the results from the recent National Lung Screening Trial (NLST). This landmark study of CT *vs.* CXR screening for lung cancer demonstrated a 20% reduction in lung cancer mortality in the CT screening arm. 39.1% of participants had at least one non-calcified nodule ≥4 mm in diameter, and 72.1% of these patients underwent further diagnostic evaluation (2). The majority of these nodules are not malignant (approximately 1% in the high-risk NLST population) and the challenge is, therefore, to find safer and more accurate ways to diagnose PPLs and avoid unnecessary surgical procedures.

No potential conflict of interest.

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The most appropriate biopsy technique for PPLs can be a challenging clinical risk-benefit decision and factors such as tumour size, location, patient co-morbidities including emphysematous changes around the PPL, respiratory function, and the pre-test probability of malignancy must be taken into account. Broadly speaking, the three general management strategies are: (I) watchful waiting with serial imaging to detect interval change, including the use of PET scans; (II) minimally invasive diagnostic procedures (bronchoscopy and transthoracic needle aspiration (TTNA)); and (III) surgical excision for diagnosis and definitive management.

CT-guided TTNA is a common method of obtaining tissue and whilst its pooled sensitivity for malignancy of 90% is impressive (3,4) it also has a false negative rate of 20-30% (5). Furthermore it is complicated by minor pneumothorax in approximately 25% of cases and major pneumothorax requiring a chest tube in 5% of cases (6). Identified risk factors for pneumothorax include smaller lesion size, deeper location, proximity to fissures and the presence of emphysema (7). Concomitant emphysema increases the pre-test probability of malignancy (if related to smoking), reduces the patient's tolerability for pneumothorax, and increases the time that intercostal catheter is needed for pneumothorax resolution. Rates of hemorrhage with TTNA are substantially higher than for bronchoscopic biopsy (8).

Of those PPLs that undergo diagnostic surgical excision, almost 20% are subsequently found to be benign, unnecessarily exposing significant numbers of patients to operative risks and reduced residual lung function (9,10). Futhermore, surgical resection has significant costs to the health system.

The diagnostic yield from transbronchial lung biopsy (TBLBx) of PPLs has incrementally increased with the addition of radiological guidance. Sampling with standard bronchoscopy under fluoroscopic guidance is associated with an overall sensitivity for malignancy between 14-63% but this is highly dependent on lesion size (<2 cm=34%, >2 cm=63%), biopsy method (forceps biopsy=57%, brush=54%, wash=43%), and number of biopsies taken (4,11). CT guided transbronchial biopsies are associated with diagnostic yields of between 65-73% but concerns about radiation exposure and inefficient use of CT scan time [in one study, an average of 4.1 scans per patients were performed with a mean effective radiation dose of 0.55 mSv (12)] has prevented widespread adoption of this technique (13).

The advent of endobronchial ultrasound radial probe (EBUS-RP), which provides a 360 degree ultrasound view of small airways and surrounding tissue, has significantly enhanced the bronchoscopic diagnostic yield for PPLs. The interface between the low density alveolated parenchyma and the solid tumour tissue is represented on ultrasound by a bright line, providing confirmation that the EBUS-RP is situated within the target lesion. With this technique Kurimoto *et al.* demonstrated diagnostic yields between 69-77%, irrespective of lesion size, and yield from lesions >3 cm was 92% (14). Paone *et al.* demonstrated the superiority of EBUS RP compared to conventional transbronchial biopsy (C-TBLBx) in a randomized study of 221 patients (97 EBUS TBLBx *vs.* 124 C-TBLBx). The sensitivity for diagnosis of malignant lesions was 78.7% in the EBUS TBLBx group compared to 55.4% in the C-TBLBx group (P=0.007); diagnostic yields were 69.2% and 78.4% for benign and malignant lesions in the EBUS TBLBx compared to 44.4% and 55.4% for benign and malignant lesions in the C-TBLBx group respectively. There was no difference in sensitivity between the two groups for lesions >3 cm, but sensitivity markedly decreased in the C-TBLBx group in lesions ≤ 2 cm (EBUS TBLBx=71% *vs.* C-TBLBx=23%, P<0.001) (15). When used with a guide sheath (GS), EBUS RP has the additional advantage of being able to tamponade the biopsy site, theoretically reducing the risk of significant hemorrhage. The diagnostic yield of EBUS is however limited by the lack of a real-time navigational system to guide the operator from the central airways to the peripheral target lesion.

The main advantage of using bronchoscopic techniques rather than transthoracic biopsy is its superior safety profile. Whilst EBUS RP can provide confirmation that the probe is located within the target lesion, further improvements in yield will only manifest once the bronchoscopist is able to steer the scope/catheter through the branching bronchial tree to the target lesion with the assistance of a navigational system. One such system is superDimension's Electromagnetic Navigation Bronchoscopy system (superDimension, Minneapolis, Minnesota).

Electromagnetic navigation bronchoscopy-description of technology

The superDimension Electromagnetic Navigation Bronchoscopy (ENB) system (inReach system, superDimension Ltd, Minneapolis, Minnesota) is a relatively new technology that provides navigational assistance coupled with steering ability to localize and sample PPLs. Initial human trials occurred in 2005 and over 20,000 procedures have since been performed (16). The system consists of: iLogic virtual bronchoscopy planning software; a "location board" which emits low frequency electromagnetic waves; an extended working channel that is similar in function to a guide sheath; an eight way steerable catheter to enable selective cannulation of bronchi; and a "locatable guide" containing sensors that allow precise tracking of both position and orientation throughout the electromagnetic field (Figure 1, 2).

Preparation and execution of ENB procedures involves several phases:

Planning phase

Procedural success is greatly influenced by accurate pre-procedure mapping of pathways leading to the target lesion, and this in turn is highly dependent on the quality of CT scans provided. CT images in Digital Imaging and Communications In Medicine (DICOM) format must be of pre-specified slice thickness, overlap and convolution kernel (all determined by brand of machine) to be loaded onto the iLogic software either from compact disk (CD) or through a network connection. The software then reconstructs these images into a multiplanar format.

The planning screen (Figure 5) consists of four panels, showing axial, coronal and sagittal CT views, and either a reconstructed three dimensional (3D) bronchial tree or virtual endobronchial view Functions such as zoom, pan, distance measurements, contrast, brightness and window level are accessible through a toolbar. The operator can navigate through the virtual endobronchial view as it would appear during bronchoscopy and the corresponding location of the virtual "tip of the bronchoscope" is tracked in all three CT views. Any point on any view can be selected and the corresponding location will be visible on the remaining views.

Six to seven easily locatable anatomical "registration points" (e.g., main and secondary carinas) are marked bilaterally for the purposes of manual registration during the actual procedure (see description of procedure below). The target lesion(s) is outlined on any of the four views and a pathway pathway from trachea to lesion is mapped by placing crosshairs over the relevant bronchus and positioning waypoints ("breadcrumbs") along bronchi

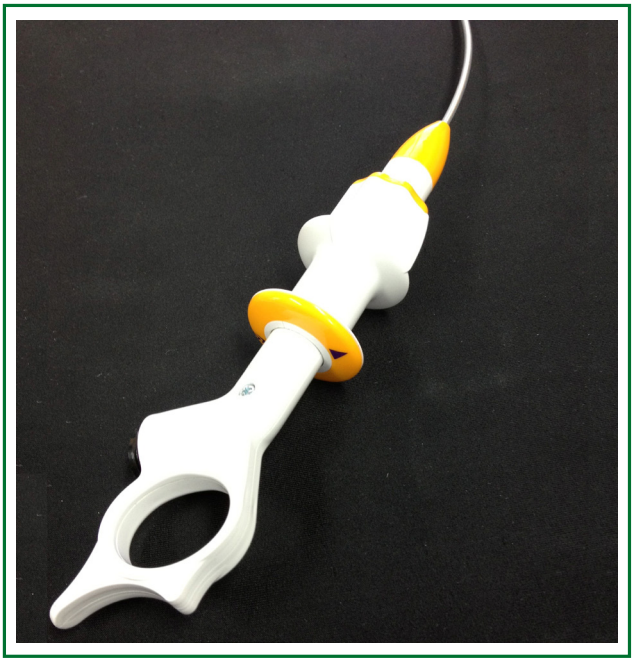

Figure 1. SuperDimension steering catheter handle: note the black arrows on the yellow ring of the catheter neck indicating the turning direction of the locatable guide.

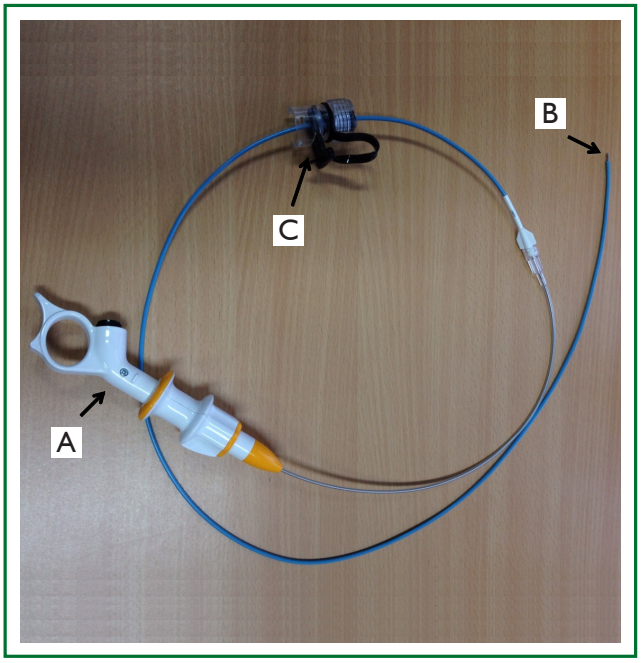

Figure 2. A: superDimension steering catheter handle; B: locatable guide housed in blue Extended Working Channel (EWC); C: EWC locking device screws onto the bronchoscope working channel port.

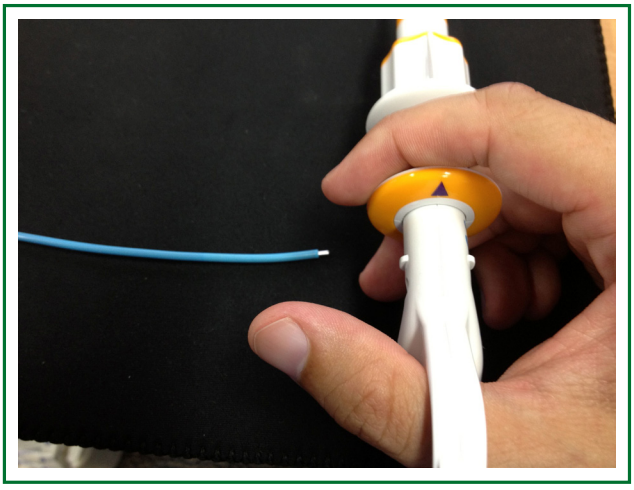

Figure 3. Catheter handle and locatable guide housed in blue Extended Working Channel - catheter in neutral position.

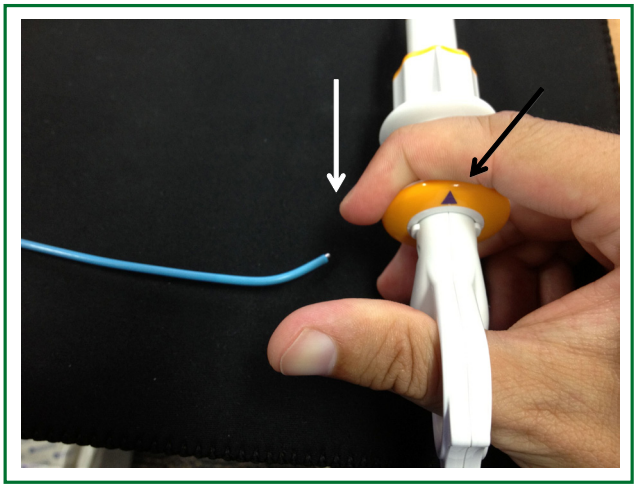

Figure 4. Squeezing of neck of catheter handle in the direction of the white arrow results in deflection of LG and EWC. The direction of deflection is controlled by turning the orange ring (black arrows) to any one of eight pre-set positions.

leading to the target lesion. Real time simultaneous location of the cross-hairs in all four viewports helps to visualize and follow paths that would otherwise appear invisible on single axial or coronal views. Once planning is complete the plotted route can be visualized on an animated virtual bronchoscopy view that replicates the exact view that will be seen during the procedure. All planning data can be saved to a removable USB drive for use with the computer located in the bronchoscopy room.

Procedure - setting up the bronchoscopy suite and patient

Consistent bronchoscopy suite set-up is imperative as metal objects and/or mobile communications devices within one metre of the electromagnetic field will reduce system accuracy.

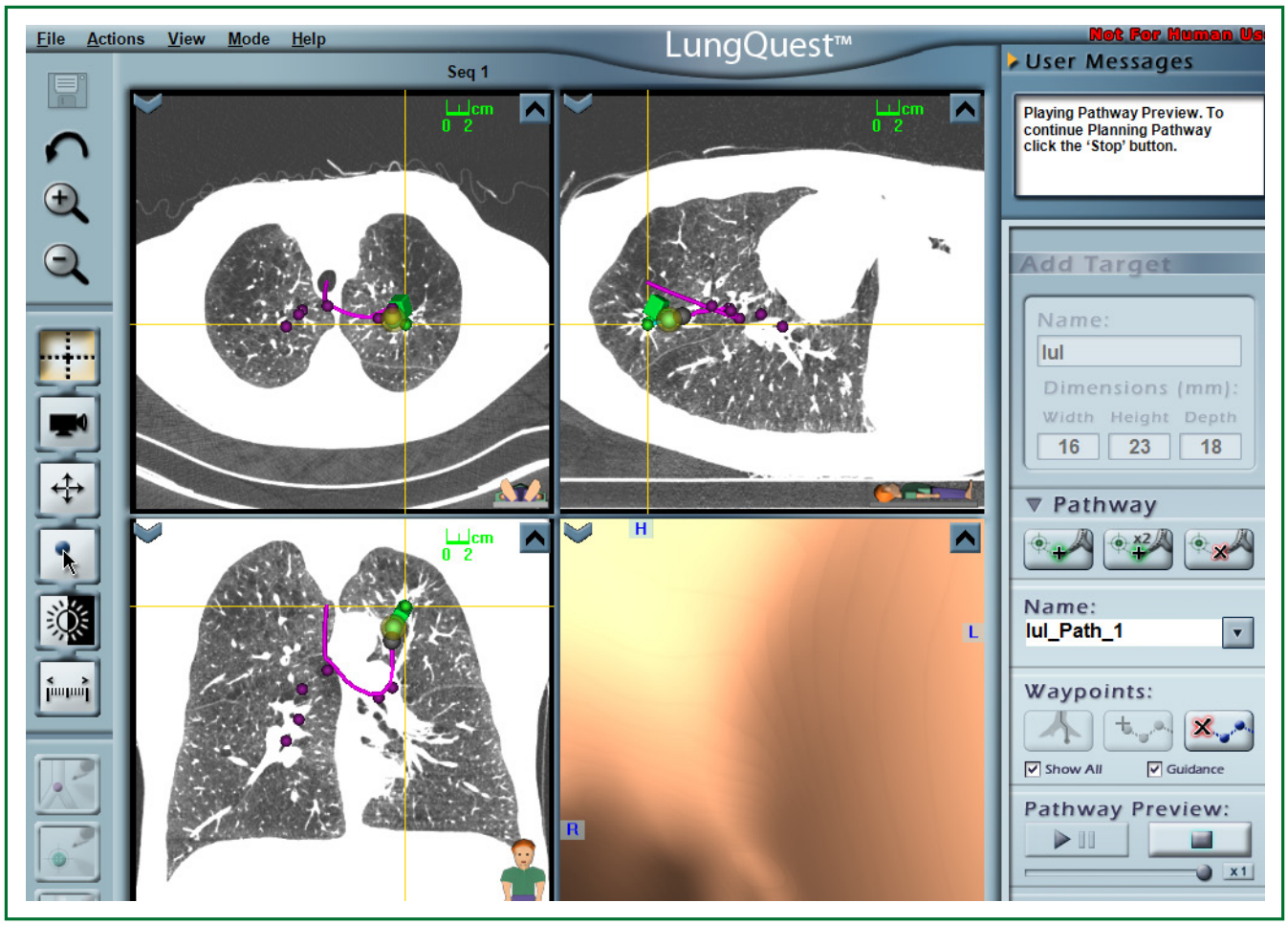

Figure 5. iLogic virtual bronchoscopy pre-planning screen. Note four viewports showing axial, coronal and sagittal CT views and virtual bronchoscopy view. Green sphere represents the target lesion, the Purple line indicates mapped pathway and purple dots represent anatomical registration points.

The location board is placed underneath the patient's mattress ensuring that the region of interest is encompassed within an imaginary rectangular prism extending 50 cm above the location board (Figure 7). Three location pads are placed in a triangular configuration on the patient's chest to enable precise tracking of the locatable guide through the electromagnetic field. Either general anaesthesia or conscious sedation may be used.

Description of procedure

After a surveillance bronchoscopy is completed to clear secretions and exclude endobronchial lesions, the extended working channel (EWC) and locatable guide (LG) are inserted through the bronchoscopic working channel until approximately 8mm of the locatable guide is visible. Registration, the process of matching the CT images to the patient's real life anatomy, can then begin either as an automated process or manually. The latest version of the iLogic software can register "automatically" obviating the need to perform manual registration. LG location and orientation data is fed back to the system at a rate of 166 times per second while the operator performs a balanced surveillance bronchoscopy. Registration accuracy is measured as the Average Fiducial Target Registration Error (AFTRE) and should be <5 mm. An AFTRE >5 mm signifies unnacceptable divergence between the CT and patient anatomy and will lead to reduced navigational accuracy (17); in this case registration should be repeated to reduce the disparity. Once enough data is collected to match CT and patient anatomy a virtual bronchoscopy image will appear and navigation can then proceed. If automatic registration fails, and with older software versions, manual registration is required. For manual registration, the operator is required to touch the LG to each of the registration points marked during the planning phase.

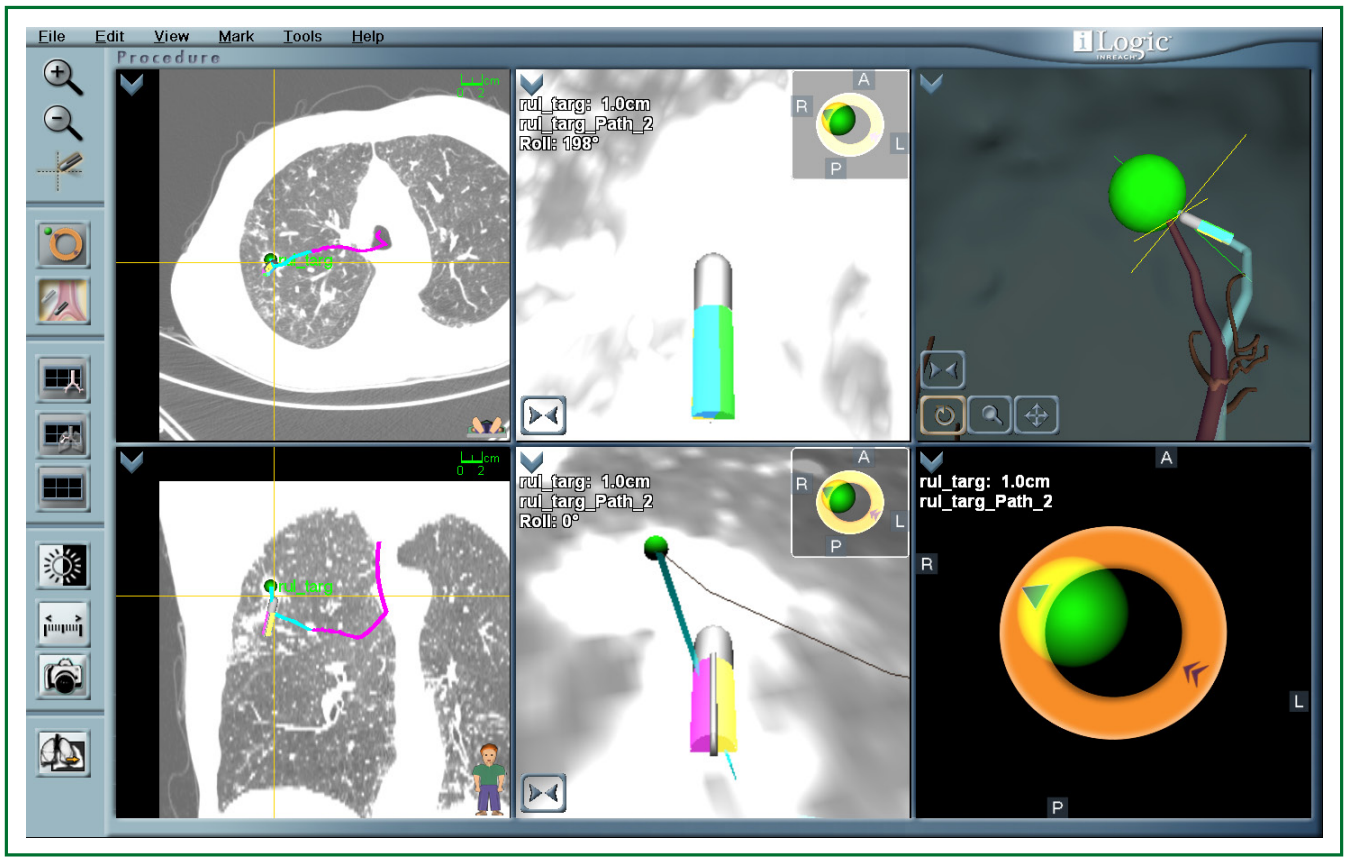

Figure 6. superDimension procedure screen showing 6 viewports. Clockwise from top left: axial CT view, MIP view, dynamic 3D view, tip view, local view, sagittal CT view. The green sphere is the target lesion and the yellow ring represents the catheter handle.

Navigation

The procedure screen can display six simultaneous views chosen by the operator (and saved as a default set up), including CT axial, CT sagittal, CT coronal, 3D static map, 3D dynamic map, tip view (a graphical representation of the steering wheel on the LG handle), 3D CT view (a planar projection of the CT volume located directly in front of the LG tip), video bronchoscope, virtual bronchoscopy, maximum intensity projection (a pseudo three dimensional projection of the CT volume below the LG tip which demonstrates high intensity structures such as blood vessels and lesions), and a local view (a planar CT image located at and aligned with the LG tip) (Figure 6). The position of the LG is displayed simultaneously in all viewports. Standard functions such as zoom, pan, measurement, and screenshot are available. The procedure screen also displays the selected target, selected pathway, and distance from the LG tip to the target centre. The planned pathway is represented by a ribbon, the colour of which changes depending on the real-time location of the LG relative to the path. Waypoints ("breadcrumbs") placed during planning are represented by coloured spheres along the pathway and the computer can provide navigational instructions to any of these locations.

The LG can be aimed in different directions by turning the handle to one of eight preset positions, denoted by two arrows on the handle, then pulling on the neck of the catheter (Figure 3, 4). The degree of flex of the locatable guide is dependent on the amount of pressure applied to the catheter neck and importantly, the flex point is approximately 14 mm proximal to the LG tip.

The bronchoscope is wedged into the subsegement leading to the target lesion and the EWC and LG are then slowly advanced with the aim of keeping the selected waypoint in the centre of the circle presented on the tip view. If the waypoint is not centred, arrows will appear on the circle edge, indicated the direction in which the LG handle needs to be turned before further advancing the EWC/LG. The size of the sphere is proportional to the distance between the planned waypoint and the LG tip.

Sampling

Once the LG tip is aligned with and in close proximity to the target lesion the EWC is locked onto the bronchoscope, the LG

Figure 7. The superDimension location board is placed underneath the patient's mattress on a metal free bed, ensuring that the target lesion will be encompassed by a rectangular prism 50 cm above the location board and the board is correctly orientated to the patient's head.

is removed, and biopsy tools are then inserted through the EWC in a fashion similar to the way a guide sheath is used during EBUS RP. Fluoroscopy or radial probe EBUS can be used to confirm EWC position in real time.

ENB is a complicated procedure requiring pre procedure preparation and skills which will be unfamiliar to experienced bronchoscopists. Although more complex than standard bronchoscopy, procedural proficiency in ENB is achievable by an experienced bronchoscopy team.

Narrative review of published literature

ENB is a relatively new technique. The first animal study was performed by Becker *et al.* in 2003 and the same group published the first human study in 2006 (18,16).

Effectiveness

The majority of published literature describes case series of PPLs biopsied with ENB. The overall published diagnostic yield for ENB alone is highly variable and ranges between 59% to 77.3%, however this includes both peripheral and mediastinal lesions in some papers (17,19-24) (Table 1). Although this yield is similar to EBUS RP, the ENB papers only occasionally describe key factors such as training and prior ENB experience, availability of EBUS, and how ENB cases were selected.

The only randomised controlled trial of ENB was published in 2007 by Eberhardt *et al.* (21). 120 patients with solitary pulmonary nodules were randomised to one of three groups: ENB alone, EBUS-RP alone, or combined ENB (to navigate) and EBUS-RP (to confirmation placement). In the combined

Table 1. Studies of ENB efficacy and safety.

Study	Year	Number of lesions	Mean Lesion Size (mm)	Upper lobe lesions (%)	Anaesthesia	Navigational Success (%)	Samples taken	Diagnostic Yield (%)	Procedure time (mean mins)	Complications
Becker (47)	2005	30	39.81	66	GA	83.3%	Forceps, brush, curette	69	Additional 9.3 minutes (total procedure time not stated)	1 Ptx 3 self limited bleeding
Hautmann (48)	2005	16 (8 infiltration, 8 SPN or mass)	22	56	Iv Midazolam, propofol	ns	Forceps, TBNA	60	Additional 8 minutes (total procedure time not stated)	Nil
Schwarz (16)	2006	13	33.5	54	Iv midazolam or propofol	ns	Forceps, brush	69	46	Nil
Gildea (49)	2006	54 peripheral	22.8 peripheral	62.5	Iv midazolam and morphine	100%	Brush 2-3 passes, TBBx 4 samples, TBNA 2-4 passes	74% (peripheral)	51	2 (3.6%) Ptx
Makris (33)	2007	40	23.5	66.5	GA	18 cases ≤8 mm from target (mean 8.7±0.8 mm from target centre)	TBBx 8.5 (mean) 6.7 specimens obtained	62.5	ns	3 (7.5%) Ptx
Eberhardt (21)	2007	39	28	56	Moderate sedation or GA	Ns	TBBx 4.1 (only forceps taken)	59	ns	2 (5%) Ptx
Eberhardt (50)	2007	92	24	56.5	GA 55 patients Iv midazolam/ fent 34 patients	Mean error 9 ±6 mm	Needle, brush, forceps (mean 5.1), or combination	67	26.9	2 (2%) Ptx 1 (1%) Perforated EWC 1 (1%) resp failure secondary to sedation
Wilson (24)	2007	279	21	50	Iv midazolam, fentanyl and propofol	95.3% mean 8±5 mm from tip to target centre	TBNA and forceps biopsy (3-4 samples)	65	ns	3 (1%) Ptx 3 (1%) mod bleeding 1 (0.3%) hematoma 1 (0.3%) pneumonia
Eberhardt (32)	2010	55	23.3	60	ns	9±5 mm	Catheter aspiration ×2 Forceps biopsy ×5	75.5	25.7	1 (1.9%) Ptx
Lamprecht (51)	2009	13	30	61.5	GA	ns	Forceps, needle brush (median 3 biopsies - none had >5)	76.9	60	Nil
Bertoletti (30)	2009	53	31.2	ns	NO/O_2 mix	10±5.9 tip to target centre	Forceps (planned 5 biopsies - actual not stated), brush	77.3	29.5	2 (4%) Ptx
Seijo (20)	2010	51	25	61	Midazolam 5 mg, fent 75 mcg (both mean)	8 mm (range, 4-9 mm) (minimum median distance from tip to target centre)	Needle, Forceps biopsy	67	56	4 (8%) mild hypoxemia

GA=general anaesthetic; Ptx=pneumothorax; ns=not stated; NO=nitrous oxide; iv=intravenous; TBBx=transbronchial biopsy; TBNA=transbronchial needle aspiration.

Figure 8. The Electromagnetic Navigation Bronchoscopy procedural computer stack situated in the bronchoscopy suite.

group, ENB navigation was repeated if the EBUS-RP was not within the target lesion. The number of navigation attempts and total procedure time were not reported. Forceps biopsy was the only sampling method used with an average of 4.1 samples taken per lesion. Despite a significantly higher mean lesion size in the ENB group (28 *vs.* 25 *vs.* 24 mm, ENB *vs.* EBUS *vs.* combined ENB-EBUS, P=0.03), diagnostic yields were 59%, 69% and 88% respectively (P=0.02). The finding of higher diagnostic yield with a multimodality procedure is intuitive - by exploiting the strengths of each technique, the operator is able to navigate to

the lesion with ENB then confirm the position within the target with EBUS RP.

Factors affecting success

Most studies of C-TBLBx for PPLs show that the presence of a "bronchus sign" (the finding of a bronchus leading directly to a peripheral pulmonary lesion) favourably impacts diagnostic yield. In a retrospective study of 65 patients with PPL undergoing bronchoscopy (FOB) with forceps biopsy and wash, Naidich found a positive bronchus sign correlated with a diagnostic yield of 60% compared with a yield of 30% in PPL with a negative bronchus sign (25).

In contrast, multivariate analysis from a study designed to evaluate predictors of success for EBUS RP guided TBLBx found that RP position relative to the lesion independently predicted yield (within lesion *vs.* adjacent to lesion *vs.* outside of lesion=83%, 61%, 4% respectively P<0.001) but underlying disease, lesion location, CT scan bronchus sign, operator or type of EBUS probe did not (26).

Only one study has investigated the effect of "bronchus sign" on ENB yield. 51 consecutive patients with pulmonary nodules from a single centre underwent ENB. Samples were obtained by alternating an aspirating needle with biopsy forceps and cytological samples immediately underwent rapid onsite cytopathology assessment (ROSE). Mean lesion size was 25 mm (15-35 mm), mean distance of 11mm from pleura, 74% had bronchus sign and most lesions were situated in the right upper lobe. Of the 34 bronchoscopies which yielded a diagnosis (67%), 30 were associated with a bronchus sign (88%). Of the 17 non diagnostic bronchoscopies, only 8 had a bronchus sign (47%) (27). Multivariate analysis identified the presence of a bronchus sign as the only variable conditioning ENB diagnostic yield (P=0.005). This result may seem slightly surprising because ENB, unlike EBUS RP, demonstrates the relationship of the LG and EWC tip to the target lesions through real time computer generated images, akin to being able to look through the walls of the airways to the target lesion. By aligning the LG/EWC with the target lesion, one could theoretically deploy an aspirating needle through the EWC, directly into the lesion, irrespective of the presence of a leading bronchus. This is one of the theoretical advantages of ENB compared to EBUS RP.

Other factors conditioning ENB yield have been reported in several case series but none has been systematically studied. Whilst Gildea *et al.* and Wilson *et al.* found no difference in yield based on lobar location, Eberhardt's multimodality study found significantly lower yields from lower lobes in the ENB group when compared to EBUS RP and combined EBUS RP/ENB (29%, P=0.01), possibly due to exaggerated respiratory motion of lesions close to the diaphragm (21,24,28). Most studies show that diagnostic yield is independent of lesion size however only small numbers have been compared and multivariate analyses have not been performed. Several studies have incorporated fluoroscopy and ROSE but it's effect on diagnostic yield, procedure time, and number of samples taken remains unknown (19,24).

Although both conscious sedation and general anaesthesia (GA) have been used in published studies, the optimal method has not been tested. In two of Eberhardt's studies, there were no statistically significant differences in diagnostic yield according to anaesthetic technique (sedation *vs.* GA 67% *vs.* 76%, P=0.28, 64% *vs.* 70%, P=0.57 (21,29)). Bertoletti found that ENB performed under an inhalational 50%/50% combination of nitrous oxide/oxygen mixture was efficacious and well tolerated (30). The optimal anaesthetic modality still needs to be identified but in the meantime, anaesthetic method will likely be determined by patient co-morbidities, lesion characteristics, operator experience and anaesthetist availability.

The lack of innovation in biopsy tools over the last forty years has contributed to a discrepancy between navigational success and diagnostic yield (17,21). Samples from PPLs at standard bronchoscopy by needle brush (a cytology brush with a needle tip) had a higher diagnostic yield than transbronchial needle aspirate, regular cytology brush or transbronchial forceps biopsy (31). superDimension have since manufactured a needle brush for use with their ENB system but no efficacy data has been published. Eberhardt and colleagues investigated the use of suction catheters as a biopsy technique. In this study, ENB was used to navigate to 55 solitary pulmonary nodules and EBUS RP was subsequently only used to assess whether or not the lesion could be visualized ultrasonographically. 75.5% of samples were diagnostic and catheter aspiration was positively correlated with success rate. Interestingly, in lesions not seen ultrasonographically, suction catheter was diagnostic in 100% compared to only 33% with forceps biopsy (32).

Safety

The biggest advantage of ENB o TTNA is its superior safety profile. Because the pleural is not breached with transbronchial biopsy, pneumothorax rates are considerably lower than TTNA and range between 0-10% (19-21,33,34.) Rare cases of minor hypoxemia and minor bleeding have been described but no deaths have been reported in the published literature.

Other potential applications

The ENB system has several other applications including placement of fiducial markers and brachytherapy catheters, guidance for transtracheal and transbronchial biopsy of mediastinal lymph nodes and peribronchial masses, and bronchoscopic pleural dye marking for localisation of lesions for

surgery.

The benefits of using ENB to place fiducial markers for stereotactic radiotherapy is becoming increasingly recognised. Treatment for inoperable lung cancer using stereotactic radio surgery rather than external beam radiotherapy allows delivery of precisely targeted radiation to the tumour while minimising dosage to adjacent tissue, but fiducial markers first have to be accurately placed, either transthoracically, intravascularly, or bronchoscopically, to enable tracking of the tumour. Despite the latter being the safest method, bronchoscopically placed markers are essentially placed "blindly" because the tumour cannot be directly visualized. Using the navigational ability of ENB may improve placement accuracy. A case series of placement of fiducial markers using ENB assisted navigation showed accurate localization in 8 of 9 cases and a 90% retention rate one week later (35). In a separate study, 234 markers were successfully placed in 52 of 60 patients. At the time of Cyberknife planning, 215/217 (99%) of the coil-spring fiducials were still in place compared to only 8/17 (58%) of linear fiducial markers. Pneumothorax rate was 5.8% (36).

Several abstracts have described the safe and efficient use of ENB to place brachytherapy catheters into inoperable lung cancers. Previously this treatment was limited to endobronchial disease as catheters were placed under direct vision but now, with the navigational capabilities of ENB, the catheters can be accurately placed into lesions outside the bronchoscopic field of view (37,38).

Challenges for clinical implementation

Whilst the theory behind ENB remains sound, several challenges still need to be addressed to enable the technology to gain widespread acceptance and dissemination.

Learning curve

ENB is a complex and lengthy procedure that involves a well functioning team operating numerous pieces of equipment and software. The ENB procedure screen provides so much information that a conscious effort is needed to focus only on those viewports providing data relevant to the current stage of the procedure. In addition, the operator needs to manipulate the navigation device whilst ensuring the bronchoscope position does not change as the EWC is advanced. Whilst case planning can be easily practiced using superDimension's LungQuest software, procedural simulation models are not yet widely available and access to the procedure screen is only possible when an LG is connected to the system. The upshot is that the learning curve is steep as procedural practice can only be gained during real life cases and the cost of consumables may limit the frequency of procedures.

The extent of the learning curve for ENB is not known. Cicenia *et al.* (abstract only) studied the diagnostic yield of 48 ENB procedures in 43 patients. Consecutive patients were placed into three groups (A, B, C) based on the chronological time they had their procedure. Both PPLs and mediastinal lesions were targeted with an average target size of 23+/–12 mm. The diagnostic yield of groups A, B and C was 58.8%, 87.5%, and 93.3% respectively, leading the authors to conclude that approximately 15 procedures are needed before obtaining procedural proficiency (39). Makris, on the other hand, found no difference in diagnostic yield between first 13/last 13 procedures and first 7/last 7 procedures in two different operators who performed 26 and 14 consecutive procedures respectively (33). In our experience the learning curve for ENB is real and can be steep. We feel that new operators would benefit from both hands-on training and procedural simulation.

Cost

As with most emerging technologies, the cost of ENB is high and its use is limited to specialized centres. The cost-effectiveness of ENB has yet to be published although two health technology assessments have been undertaken. The Blue Cross of Idaho has performed a series of systematic reviews on its utility and have concluded that currently there is insufficient evidence to determine the risks and benefits of ENB when compared to standard approaches to diagnose peripheral lesion (40). The data are also insufficient to identify which patients might benefit from ENB. A policy statement from AETNA, an American health insurance company, stated that "Even though the technologies are very attractive and pilot data are extremely encouraging, more studies establishing selection criteria and best utility are needed" (41).

Planning CT scan issues

The success of ENB is to a large extent dependent on the quality of the pre-procedure CT scan. Factors such as poor inspiratory effort or motion artifact result in suboptimal airway visualization, potentially concealing otherwise appropriate pathways and resulting in lower diagnostic yields. The superDimension ENB system demands very specific CT parameters (slice thickness, slice interval, slice overlap, convolution kernel) in order to create a three dimensional bronchial tree for optimal navigation. Typically, however, a patient is referred to a specialist clinic only after their general practitioner has ordered a CT scan, usually with parameters that are incompatible with the iLogic software. Furthermore, most radiology practices do not store the raw CT data for more than a week, making iLogic compatible image reconstruction impossible. In these cases, for ENB to be used, the patient would need to undergo a repeat CT scan with the

resultant additional radiation exposure. To avoid this duplication, it is essential that radiologists and general practitioners are aware that ENB technology is available so they can store and retrieve the raw DICOM data to reconstruct iLogic compatible CT scans.

Areas for research

The first animal trials of ENB were performed in 2003 yet few randomised controlled trials have been performed, leaving uncertainty about the place of ENB in the diagnostic algorithm for PPLs. Pressing issues include when to choose ENB over TTNA for diagnosing PPLs and whether ENB is useful after failed EBUS-RP. Although multimodality procedures are associated with higher diagnostic yields, the cost of ENB makes it unlikely that combined EBUS/ENB procedures will become routine for every PPL. It will also be important to compare ENB with other ancillary techniques such as virtual bronchoscopy (VB) and ultra thin bronchoscopy. Comparative studies are needed to assess the role of ENB in the placement of fiducial markers for stereotactic radiotherapy, and evaluate newer sampling tools such as the needle brush. Predictors of diagnostic yield, aside from the "bronchus sign", also need to be delineated to optimize patient selection, improve diagnostic yield and minimise complications.

Refinement of ENB hardware and software is constantly occurring. Most of the published research to date was performed using older versions of the iLogic software which required manual registration. The most recent software version defaults to automatic registration whereby the operator performs a balanced survey of the bilateral bronchial tree rather than touching several pre-defined points to align the CT images with real time anatomy. The accuracy of this "automatic registration" algorithm has never been studied. Similarly if new steering mechanisms or locatable guides become available, their safety and efficacy will need to be restudied which may in turn hinder widespread adoption.

EDoes enb add value to our current guided bronchoscopic biopsy techniques?

Direct comparisons between guided bronchoscopic techniques and TTNA are difficult due to variation in definition of PPLs, lesion location, methods of case selection, and biopsy methods. Other factors that need to be considered when selecting the appropriate diagnostic modality include type of equipment available, local expertise and patient characteristics.

Several studies have attempted to compare the various guided bronchoscopic techniques. In a randomized controlled trial of EBUS RP with guide sheath (GS) *vs.* CT TTNA, no significant overall difference in diagnostic yield was observed but CT TTNA had a superior yield in lesions less than 2 cm. Pneumothorax rate was higher with CT TTNA and patient satisfaction favoured EBUS RP (42). In Japan, The V-NINJA group randomized peripheral lesions ≤3 cm to EBUS RP with GS with or without navigational assistance from VB. The diagnostic yield was significantly higher in the VB group (80.8% *vs.* 67.4% P=0.032), driven primarily by successful diagnoses in lesions ≤2 cm. Total examination time and time to initial biopsy were both shorter in the VB group (43). A meta-analysis and systematic review of EBUS RP for diagnosis of peripheral pulmonary lesions that included 16 studies with 1,420 patients found an overall sensitivity of 0.73 (95% CI 0.70-0.76) for detection of lung cancer. There was significant inter-study heterogeneity most likely due to prevalence of malignancy, lesion size, and reference standard used (44). Wang Memoli *et al.* recently published a meta-analysis of guided bronchoscopy including studies of VB, ENB, GS, ultra thin bronchoscopy (UTB) and EBUS RP (45). All methods were safe with an adverse event rate of only 1.6% (mostly pneumothorax). Pooled diagnostic yield was 70%. VB, EBUS RP and GS had higher yields than average (VB=72%, EBUS RP=71.1%, GS=73.2%) whereas ENB had the lowest weighted diagnostic yield (67%).

Conclusions

Electromagnetic navigation bronchoscopy is gaining increasing acceptance as a diagnostic modality, particularly in North America and Europe. Currently, high level evidence underpinning the technique is limited and its position in the diagnostic algorithm of PPLs remains unclear. This was reflected in the 2011 British Thoracic Society bronchoscopy guidelines and the 2007 ACCP lung cancer guidelines (4,46). The cost of ENB is also a major drawback (46). On the other hand, it is a relatively new technology and the evidence base will no doubt mature over time. Modifications in hardware and software continue with the hope of improved diagnostic yield and user friendliness however each innovation demands independent evaluation. Ultimately, high level research directly comparing diagnostic yield of ENB to CT TTNA in patients who have failed EBUS RP, comparison of ENB against other techniques such as ultra thin bronchoscopy and virtual bronchoscopy, are required as well as studies examining predictors of success in order to clarify utility and place in diagnostic algorithm.

Despite the challenges outlined above together with high cost and learning curve, the navigational ability of ENB offers the potential for wider clinical applicability, both diagnostic and therapeutic, than is possible with conventional bronchoscopy.

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